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(57) Abstract: The present invention relates to new rosuvastatin formulations prepared so as to be used in the treatment of hyperlipidemia. The characteristic features of the formulations are that a pharmaceutically acceptable phosphate salt is used as the stabilizer and the ratio of rosuvastatin to the stabilizer in the formulation is in the range of 0.5-20 by weight.



WO 2011/139256 A2

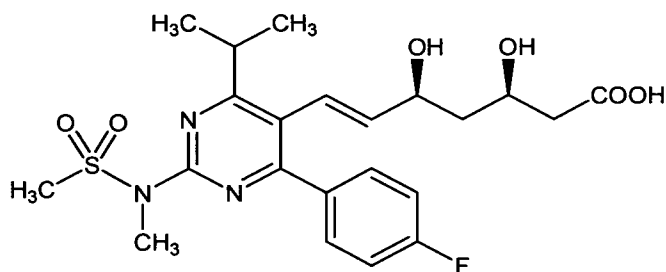
STABLE ROSUVASTATIN FORMULATIONS

The present invention relates to new rosuvastatin formulations prepared so as to be used in the treatment of hyperlipidemia. The characteristic features of the formulations are that said formulations comprise rosuvastatin on effective amounts; a pharmaceutically acceptable phosphate salt is used as the stabilizer, and the ratio of rosuvastatin to the stabilizer in the formulation is in the range of 0.5-20 by weight.

Background of the Invention

Cardiac disease is the leading cause of death in the world. In general, one of the most significant factors for these diseases is total/high density lipoprotein (HDL) cholesterol ratio.

Therefore, there is need for new developments in the treatment of dyslipidemia. Researchers have found rosuvastatin, the newest statin, which was first disclosed in the patent numbered US5260440 (A) by SHIONOGI & CO. Rosuvastatin which has the chemical name (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2[methyl(methylsulphonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid is a HMG CoA enzyme inhibitor and it is displayed in formula (I):



(I)

It is indicated that rosuvastatin, which is displayed in formula (I) in the patent numbered US5260440, inhibits the activation of the enzyme named HMG-CoA reductase that is responsible for cholesterol synthesis in the body and prevents cholesterol formation and it is effective in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

Statin derivative cholesterol absorption inhibitors can also be used in combination with cardiovascular active agents; for instance fibric acid derivatives, calcium channel blockers and cholesterol absorption inhibitors.

It has been explained in various publications that the cholesterol lowering effect of statins synergistically increases with cholesterol absorption inhibitors:

- Davis HR, Pula KK, Alton KB, Burrier RE & Watkins RW. The Synergistic Hypocholesterolemic Activity of the Potent Cholesterol Absorption Inhibitor, Ezetimibe, in Combination with 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Dogs. *Metabolism* 2001; 50(10):1234-1241
- Sudhop T, Von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* 2002; 62(16):2333-47
- Gagné C, MD; Gaudet D, MD PhD; Bruckert E, MD PhD. Efficacy and Safety of Ezetimibe Coadministered With Atorvastatin or Simvastatin in Patients With Homozygous Familial Hypercholesterolemia. *Circulation* 2002; 105; 2469-2475

The product named INEGY® which comprises rosuvastatin and ezetimibe as the active agents and marketed by MERCK can be given as an example for the combination of statins and cholesterol absorption inhibitors.

However, when the prior art is taken into consideration, it is seen that rosuvastatin easily disintegrates as affected by factors such as moisture and light, and this constitutes a serious impediment to development of stable rosuvastatin formulations and combinations. Rosuvastatin calcium is transformed into lactone as a result of “intramolecular esterification” which occurs between carboxylic acid in its structure and hydroxyl groups on β and δ carbons of this carboxylic acid. The reaction takes place in acidic environment and the basic agents cause the reaction to revert back. The main disintegration products (3R, 5S) that arise as a result of the disintegration of rosuvastatin are lacton and oxidation products. This characteristic reduces the stability of the substance and therefore, shortens the shelf life. Thus, neither the pharmaceutical formulations comprising rosuvastatin alone or the combinations comprising rosuvastatin and one or more active agents can be produced effectively.

There exist documents for solution of this problem in the prior art.

The patents numbered WO 01/54668 and WO 01/54669 are formulation patents belong to the product known as “Crestor®” on the market. It was indicated in the description part of the patents that adjusting only the pH value does not suffice to bring a solution for the problem stated above. In addition, use of tribasic calcium phosphate, tribasic magnesium phosphate, tribasic aluminum phosphate salts in order to stabilize rosuvastatin calcium compositions was defined in said patents. In the product named “Crestor®” which is available on the market, there is a high amount of tribasic calcium phosphate as the stabilizing agent.

Richter Gedeon NYRT disclosed formulations comprising rosuvastatin calcium as the active agent and calcium acetate, magnesium hydroxide, calcium gluconate, calcium glycerophosphate or aluminum hydroxide as the stabilizing agent in the patent application WO2008035128(A1).

Since rosuvastatin has a high tendency to disintegrate in acidic pH, all the solutions in the prior art are based on keeping the pH of the solution at least 8 or above. As can be seen in the examples given above, it is quite common to use various alkaline agents in order to provide stability in rosuvastatin formulations. However, high amounts of alkaline agent intake especially in medicaments such as cardiac drugs which are taken at least once a day gives harm to gastric mucosa and causes serious stomach problems in patients. Thus, there is need for new and stable formulations for the most effective and the most frequently used medicament of statin group.

Description of the Invention

The first aspect of the invention relates to an enhanced pharmaceutical formulation comprising rosuvastatin in a therapeutically effective amount and a pharmaceutically acceptable phosphate salt as the stabilizer. The invention discloses stable rosuvastatin formulations which have longer shelf life than known formulations and in which the ratio of rosuvastatin to the stabilizer is in the range of 0.5- 20 by weight.

The characteristic feature of the formulations is that said formulations comprise rosuvastatin in an effective amount, a pharmaceutically acceptable phosphate salt and/or pharmaceutical derivatives thereof, and the ratio of rosuvastatin to the stabilizer is in the range of 0.5-20 by weight.

Another characteristic feature of the formulations of the present invention is that the ratio of rosuvastatin to the stabilizer used in said formulations is preferably in the range of 0.5-15,

more preferably in the range of 0.5-8 by weight. The term "phosphate salt" used throughout the text comprises phosphate salts and all pharmaceutically acceptable derivatives thereof. 'Derivatives' refers to all pharmaceutically acceptable hydrates and anhydrides of said phosphate salt. Said phosphate salts can be selected from a group comprising monobasic, 5 dibasic or tribasic calcium, magnesium, aluminum, iron phosphate salts and/or hydrates thereof. The preferred phosphate salt is in dihydrate form though it is more preferably dibasic calcium phosphate dihydrate and/or pharmaceutically acceptable derivatives thereof.

Rosuvastatin used in the formulations of the present invention is in the form of pharmaceutically acceptable salt thereof, preferably in calcium salt form.

10 Rosuvastatin calcium is used in a particular particle size range in formulations of the present invention. D(50) particle size for rosuvastatin calcium is in the range of 5 to 80 micron, preferably in the range of 20 to 80 micron, more preferably in the range of 30 to 80 micron; D(90) particle size is in the range of 100 to 400 micron, preferably in the range of 100 to 350 micron, more preferably in the range of 100 to 300 micron.

15 The term "D(50) particle size" used in the text refers to the particle size of 50% of rosuvastatin particles by volume and "D(90) particle size" refers to the particle size of 90% of rosuvastatin particles by volume, which were measured in the device Malvern Mastersizer 2000 S (Scirocco 2000) by dry method. The formulations according to the present invention can comprise at least one sterol absorption inhibitor in an effective amount as a second active 20 agent.

The sterol absorption inhibitor used in rosuvastatin formulations of the present invention is selected preferably from ezetimibe and/or its pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline and amorphous forms and/or combinations thereof.

25 The formulations of the present invention comprise;

- the active agent/agents in the range of 1% to 30% by weight,
- at least one pharmaceutically acceptable diluent in the range of 20% to 85% by weight,
- a pharmaceutically acceptable stabilizer in the range of 1% to 5% by weight,
- 30 • at least one pharmaceutically acceptable disintegrant in the range of 5% to 20% by weight,

- one or more pharmaceutically acceptable excipients in the range of 1% to 20% by weight.

In addition to the substances listed above, the formulations can optionally comprise coating materials.

5 In the formulations of the present invention, substances such as antioxidants, chelating agents, alkalinizing agents and photoprotectives can be used as the stabilizer. The stabilizer/stabilizers used in the formulations of the present invention are preferably alkalinizing agents and they can be selected from, but not limited to, a group comprising alkaline metal salts such as sodium carbonate, sodium hydrogen carbonate, sodium hydroxide,
10 sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulfate, magnesium acetate, magnesium silicate, magnesium aluminate; and organic compounds such
15 as primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzyl ethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacryline sodium, sodium alginate and/or pharmaceutically acceptable hydrates and/or derivatives thereof.

The formulations of the present invention can comprise other pharmaceutically acceptable components such as additives and excipients selected from a group comprising binders,
20 disintegrants, viscosity enhancing agents, filling materials, desiccants, lubricants, diluents, binders, glidants, wetting agents, anti-adhesive agents, solvents, sweeteners.

The filling materials used in the present invention comprise one or more components selected from the group comprising lactose, sugar, starch, modified starch, mannitol, sorbitol, inorganic salts, microcrystalline cellulose, cellulose, calcium sulfate, xylitol and lactitol.

25 The disintegrant of the present invention enables the dosage form to disperse easily and rapidly in water and it is significant from this aspect. The disintegrants can be selected from polymers having high disintegrating characteristics such as cross-linked hydroxypropyl cellulose, polyvinylpyrrolidone, high molecular weight polymers, microcrystalline cellulose, sodium starch glycolate, povidone, crospovidone or colloidal silicone dioxide, alginic acid,
30 sodium alginate, corn starch. According to the present invention, the disintegrant preferred is crospovidone and its amount in the formulation is in the range of 5% to 20%.

The anti-adhesive substances of the present invention are used in order to prevent the mixture comprising active agent to adhere on device and machine surfaces during the process and create a rough surface. The substances used for this purpose comprise one or more components selected from the group comprising talc, colloidal silicon dioxide (Aerosil, Syloid, Cab-O-Sil), magnesium stearate and corn starch.

The binders of the present invention comprise one or more components selected from the group comprising potato starch, wheat starch or corn starch; microcrystalline cellulose, for instance Avicel®, Filtrak®, Heweten® or Pharmacel® products; hydroxypropyl cellulose, hydroxyethyl cellulose; hydroxypropylmethyl cellulose, for instance hydroxypropylmethyl cellulose- Tip 2910 USP; hypromellose and polyvinylpyrrolidone, for instance Povidone® K30(BASF); lactose, guar gum, pectin, gelatin, sodium alginate.

The lubricants of the present invention comprise one or more components selected from the group comprising metallic stearates (e.g. magnesium stearate, calcium stearate, aluminum stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffines, hydrogenated vegetable oil, leucine, polyethylene glycols (PEG), metallic lauryl sulfates (e.g. sodium lauryl sulfate, magnesium lauryl sulfate), sodium chloride, sodium benzoate, sodium acetate and talc and/or hydrates thereof. The lubricant used in the formulations of the present invention is preferably magnesium stearate.

The diluents of the present invention comprise one or more components selected from the group comprising alkaline metal carbonates, cellulose derivatives (e.g. microcrystalline cellulose, cellulose acetate etc.), dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, lactose, direct compression-lactose, maltose, mannitol, simethicone, sorbitol, starch, talc, xylitol and/or hydrates and/or derivatives thereof. The diluent used in the formulations of the present invention is preferably direct compression-lactose.

The solvents of the present invention comprise one or more components selected from the group comprising toluene, benzene, acetone, methyl acetate, tetrahydrofuran, heptanes, hexane, acetonitrile, alcohol and/or alcohol mixtures.

The film coating material of the present invention is composed of lactose, hydroxypropyl methyl cellulose, triacetine, titanium dioxide, polyvinyl alcohol, talc, lecithin, polyethylene glycol and/or mixtures thereof. Quality of the coating material plays an important role in

maintaining the stability of formulations comprising rosuvastatin during shelf life. The coating material according to the present invention comprises sufficient amounts of talc, lecithine and optionally at least one of the components listed above or mixtures of these components in addition.

- 5 The coating material used to coat the tablet dosage form of the present invention is approximately in the range of 0.5% to 10% of the total tablet weight, preferably in the range of 1% to 5%.

Apart from the ones listed, other additives and excipients can optionally and purposefully be added into the formulations of the present invention. The pharmaceutical formulations to be
10 administered orally can be in tablet, capsule, soluble tablet, effervescent tablet, chewable tablet, coated tablet, soluble granule, soluble powder, emulsion, suspension, solution form.

The oral dosage form according to the present invention is preferably film coated tablet and the formulations of the present invention can be produced by any production method known in the prior art.

- 15 The process preferred for production of film coated tablet formulations comprising rosuvastatin calcium as the active agent according to the present invention is as follows:

1. Rosuvastatin calcium at a particular particle size, at least one pharmaceutically acceptable disintegrant, the diluent and the stabilizer are mixed,
2. The obtained mixture is sieved preferably through a 25 mesh sieve and treated with
20 the lubricant,
3. The final mixture is sent to the compression machine and tablets are compressed by imposing a compression force in the range of 10 kN to 200 kN, preferably in the range of 30 kN to 200 kN, more preferably in the range of 30 kN to 150 kN,
4. The compressed tablets are film coated by the coating material obtained dissolving the
25 sufficient amount of coating material in deionized water.

The examples below are given to explain the present invention. These examples are evaluated with the description part given in detail hereinabove but they do not restrict the scope of said invention.

EXAMPLES

In order to prepare the formulations given in the examples, rosuvastatin calcium, dibasic calcium phosphate dihydrate, the disintegrant and the diluent are mixed and sieved. Magnesium stearate is added into the mixture obtained and the blend is mixed again. The final mixture is loaded to tablet compression machine and tablets are compressed imposing 80 kN compression force. The compressed tablets are coated with the film coating solution prepared by dissolving the coating material in a sufficient amount of deionized water in advance and the tablet formulations are finalized.

1) Tablet formulation comprising rosuvastatin calcium

CORE		
Content	Function	Percentage (%) of Weight
Rosuvastatin Calcium	Active agent	13.60
Dibasic Calcium Phosphate Dihydrate	Stabilizer	1.95
Crospovidone	Disintegrant	9.50
Magnesium Stearate	Lubricant	1.60
Direct compression-lactose	Diluent	71.35
COATING		
Content	Percentage (%) of Weight	
Film Coating Material	2.00	
Total	100	

$$\text{Percentage by weight} = \frac{\text{Rosuvastatin Calcium (\% weight)}}{\text{Stabilizer (\% weight)}} = \frac{13.60}{1.95} = 6.97$$

• **2) Tablet formulation comprising ezetimibe and rosuvastatin calcium**

For the combination tablet to be prepared according to the formulation given below, two active agents are formulated separately, and then the two mixtures obtained are mixed. The final mixture is loaded to tablet compression machine and tablets are compressed. The tablets prepared are film coated.

Content	Function	Percentage (%) of Weight
Ezetimibe	Active Agent	2.45
Direct Compression-Lactose	Diluent	49.50
Hydroxy Propyl Methyl Cellulose	Binder	0.75
Croscarmellose Sodium	Disintegrant	2.00
Microcrystalline Cellulose	Diluent	4.40
1-propanol	Solvent	In Sufficient Amount
Rosuvastatin Calcium	Active Agent	5.15
Direct Compression-Lactose	Diluent	24.35
Dibasic Calcium phosphate Dihydrate	Stabilizer	1.45
Crospovidone	Disintegrant	6.00
Microcrystalline Cellulose	Diluent	1.45
Magnesium Stearate	Lubricant	1.10
Colloidal Silicon Dioxide	Anti-adhesive agent	0.15
COATING		
Content	Percentage (%) of Weight	
Film Coating Material	1.25	
Total	100	

$$\text{Percentage by Weight} = \frac{\text{Rosuvastatin Calcium (\% weight)}}{\text{Stabilizer (\% weight)}} = \frac{5.15}{1.45} = 3.55$$

CLAIMS

1. A rosuvastatin formulation used by the oral route characterized in that a pharmaceutically acceptable phosphate salt and/or a pharmaceutically acceptable derivative thereof is used as the stabilizer in said formulation and the ratio of rosuvastatin to the stabilizer in said formulation is in the range of 0.5-20 by weight.
2. The formulation according to claim 1, wherein the stabilizer in the formulation is in dihydrate form.
3. The formulation according to claim 1, wherein the stabilizer in the formulation is a dibasic phosphate dihydrate salt.
4. The dibasic phosphate dihydrate salt according to claim 3, wherein said dibasic phosphate dihydrate salt is one of calcium, magnesium, aluminum, iron salts.
5. The dibasic phosphate salt according to claim 4, wherein said dibasic phosphate salt is dibasic calcium phosphate dihydrate.
6. The formulation according to claim 1, wherein the ratio of rosuvastatin to the stabilizer in the formulation is in the range of 0.5 to 15 by weight.
7. The formulation according to claim 1, wherein the ratio of rosuvastatin to the stabilizer in the formulation is in the range of 0.5 to 8 by weight.
8. The formulation according to claim 1, wherein said formulation comprises a pharmaceutically acceptable diluent.
9. The diluent according to claim 8, wherein said diluent is selected from a group comprising alkaline metal carbonates, cellulose derivatives, dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, lactose, direct compression-lactose, maltose, mannitol, simethicone, sorbitol, starch, talc, xylitol and/or hydrates and/or derivatives thereof.
10. The diluent according to claim 9, wherein said diluent is preferably direct compression-lactose.
11. The formulation according to claim 1, wherein said formulation comprises pharmaceutically acceptable excipients in addition to rosuvastatin and the stabilizer.
12. The formulation according to claim 11, wherein said formulation is composed of ;
 - Rosuvastatin calcium in the range of 1% to 30%
 - Direct compression-lactose in the range of 20% to 80%
 - Dibasic calcium phosphate dihydrate in the range of 1% to 5%

- Crospovidone in the range of 5% to 20%
- One or more pharmaceutically acceptable excipient in the range of 1% to 20%.

13. The formulation according to claim 1, wherein said formulation comprises a second active agent.

5 14. The formulation according to claim 13, wherein said formulation preferably comprises at least one sterol absorption inhibitor and/or its pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof as a second active agent.

10 15. The formulation according to claim 14, wherein sterol absorption inhibitor is preferably ezetimibe.